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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s): Theodore Sana

Serial No.: 10/001,688 **Examiner:** Theodore Sana

Filing Date: October 25, 2001 **Group Art Unit:** 1637

Title: COMPOSITIONS AND METHODS FOR OPTIMIZED HYBRIDIZATION USING MODIFIER SOLUTIONS

COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria VA 22313-1450

TRANSMITTAL OF REPLY BRIEF

Sir:

Transmitted herewith is the Reply Brief with respect to the Examiner's Answer mailed on 11-01-2005 This Reply Brief is being filed pursuant to 37 CFR 1.193(b) within two months of the date of the Examiner's Answer.

(Note: Extensions of time are not allowed under 37 CFR 1.136(a))

(Note: Failure to file a Reply Brief will result in dismissal of the Appeal as to the claims made subject to an expressly stated new grounds of rejection.)

No fee is required for filing of this Reply Brief.

If any fees are required please charge Deposit Account 50-1078.

Respectfully submitted,

Theodore Sana

By _____

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Attorney/Agent for Applicant(s)

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Date: 12-30-2005

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REPLY BRIEF Address to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Application Number	10/001,688
	Confirmation Number	3172
	Attorney Docket No.	10010819-1
	Filing Date	October 25, 2001
	First Named Inventor	Theodore Sana
	Examiner	Joyce Tung
	Group Art	1637
	Title: *Compositions and Methods for Optimized Hybridization Using Modifier Solutions*	

Sir:

This Reply Brief is in response to the Examiner's Answer mailed by the Office on November 1, 2005.

Please charge any required fees to Deposit Account No. 50-1078, order number 10010819-1.

REPLY BRIEF

In this Reply Brief, the Appellants address several issues raised in the Examiner's Answer. The Appellants note that all arguments presented in the prior Appeal Brief still apply with equal force, but are not reiterated here solely in the interest of brevity and for the convenience of the Board.

In this Reply Brief, the Appellants address specific assertions made by the Examiner in responding to Appellants' arguments. The Examiner's assertions are addressed in four sections below, each section representing a separate and independent reason why the remaining rejections should be withdrawn.

Brenner teaches away what is being claimed

As discussed in the Appeal Brief, the claims are directed to microarray-based based hybridization methods that employ urea.

The claims are rejected as obvious in view of Brenner and Oliva.

However, MPEP § 2145 X.D.2 is explicitly clear: references cannot be combined where a reference teaches away from their combination. In other words, it is improper to combine references where the references teach away from their combination. *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983).

The Appellants argued that Brenner teaches away from what is being claimed because Brenner explicitly warns against the use of reagents that alter base-specific stability of nucleic acid duplexes (of which urea would be an example) in hybridization assays. Specifically, in lines 22-28 of col. 2, Brenner warns that the use of reagents that alter base-specific stability of nucleic acid duplexes would be undesirable because their **effects are limited** and can be **incompatible** with further manipulations. Further, in lines 44-50 of col. 2, Brenner presents his invention as a system which "minimized the occurrence of false positives and false negative signals **without the need to employ special reagents for altering natural base pairing**". (Emphasis added). It is clear from Brenner's disclosure that Brenner seeks to avoid adding reagents that alter base-specific stability of nucleic acid duplexes.

On the basis of Brenner's extensive warnings about adding agents that alter base pairing to hybridization buffer, one of skill in the art would not combine urea, an agent that alters base pairing, into Brenner's methods.

On lines 6-9 of page 6 of the Examiner's Answer, the Examiner does not disagree with Brenner's statement. Instead, the Examiner has attempted to dismiss the Appellants' arguments by asserting that because Brenner does not specifically indicate that urea would be an undesirable agent, Brenner does not teach away from what is being claimed. In other words, the Examiner argues that because Brenner does not specifically state "do not use urea", there is no teaching away.

The Appellants acknowledge that Brenner does not specifically mention urea as an undesirable agent. However, the Appellants submit that at the time of filing, Brenner's warnings about the use of base-stabilizing agents in array-based hybridization assays would have clearly encompassed urea. As such, the teachings of Brenner would have been read by one of skill in the art as a teaching away from using urea.

Thus, the Appellants prior arguments still stand with equal force. The Appellants submit that all remaining rejections may be withdrawn on this basis alone.

The claimed subject matter provides unexpected results

In addition to the above argument, the Applicants have also argued that the use of urea in a hybridization buffer for array-based assays provides unexpectedly good results, as compared to other compounds that are known to modify the kinetics of hybridization.

The Appellant's showing is supported by data (as supplied in Appendix A of Appeal Brief) that unequivocally demonstrates that microarrays hybridized using a urea-based hybridization buffer provide better results than microarrays hybridized in other denaturants, i.e., salt (e.g., SSC and SSPE), and two different concentrations of formamide. This result was unexpected, and could not have been predicted by the teachings of Brenner or Oliva.

Citing M.P.E.P. § 2144.08 (citing *In re Dillon*, 16 U.S.P.Q. 2d 1897, 1901 (Fed. Cir. 1990) and *In re Geisler*, 43 U.S.P.Q.2d 1362, 1365 (Fed. Cir. 1997)), the

Appellants have argued that this showing of unexpected results should be sufficient to permit withdrawal of this rejection.

On lines 14-18 of page 6 of the Examiner's Answer, the Examiner has attempted to dismiss the Appellants' arguments by simply saying that the claimed invention does not provide an unexpected result in view of Oliva.

In response, the Appellants note that Oliva does not report any experiment in which different denaturants are tested to determine their effect on hybridization. In contrast to the Examiner's submission, the superiority of urea over other denaturants could not have been predicted from Oliva's disclosure.

Thus, the Examiner's argument in the Reply Brief is ungrounded and, as such, the Appellants' prior arguments still stand with equal force.

The Appellants note that Oliva's Table 1 reports the effect of various reagents on EGFP (enhanced green fluorescent protein) activity in fixed cells, not the effects of those agents on nucleic acid hybridization.

Brenner and Oliva are in non-analogous arts;

In the Appeal Brief, the Appellants also argued that the teachings of Oliva and Brenner are in non-analogous arts. As such, the teachings of Oliva and Brenner cannot be combined, under current law, to render the appealed claims obvious.

MPEP 2141.01(a) prescribes that in order for the teachings of two references to be analogous, the teachings should be related by function and structure.

The Appellants submit that the teachings of Brenner and Oliva are not related by either function or structure, and, as such, they should be considered non-analogous.

Functionally, Brenner teaches a method for sorting oligonucleotide-tagged molecules that employs an oligonucleotide array. Oliva's method, on the other hand, is a method for obtaining an expression pattern of a single RNA in a sectioned tissue. Brenner and Oliva's function (i.e., purpose) is therefore entirely different.

Structurally, Brenner's method includes labeling a population of molecules with oligonucleotide tags and hybridizing the oligonucleotide tag-labeled molecules to an array containing oligonucleotides that are complementary to the oligonucleotide tags. The hybridizing polynucleotides are then sequenced. Oliva's

method, on the other hand, includes making a labeled RNA, hybridizing that RNA to the RNA of a tissue section, and then observing the pattern of RNA/RNA duplexes in the tissue section.

While both Brenner's and Oliva's methods do both involve nucleic acid hybridization, the Appellants note that different types of target labeled nucleic acids are employed (DNA verses RNA), different types of probe nucleic acids are employed (DNA verses RNA), different types of nucleic acid duplexes are produced (RNA/RNA verses DNA/DNA), different types of substrate are used (an array of DNA oligonucleotides verses a tissue section containing mRNA species) and completely different hybridization conditions are employed. In structural terms, Brenner and Oliva's methods are entirely different.

In view of the above, the Appellants submit that Brenner and Oliva are completely different structurally and functionally, and, as such should be considered non-analogous.

On page 5, line 18-20 of the Appeal Brief, the Examiner attempted to dismiss the Appellants' arguments by asserting that the Appellants' arguments do not relate to any elements in the appealed claims.

This is not the case. The instant claims relate to methods that include hybridizing a probe to *oligonucleotides* that are *covalently linked* to the surface of a *microarray*. All of these elements are present in the appealed claims and, as discussed above, are not present in Oliva's disclosure.

In view of the above, the Appellants maintain their position that Oliva is non-analogous art.

No motivation exists to combine Brenner and Oliva

Finally, in the Appeal Brief, the Appellants argued that no motivation to combine the disclosures of Brenner and Oliva exists.

In the Examiner's Answer, the Examiner stated that motivation to combine Brenner and Oliva is found in Oliva, because Oliva states that urea can lower the annealing temperature of a hybridization reaction.

However, Oliva makes no specific suggestion to use urea in array-based assay. In view of this deficiency, the Applicants submit that Oliva *does not* provide any suggestion to combine the cited references.

Neither of the cited referenced recognizes any problem that would be solved by the addition of urea to an array-based hybridization assay. The problem solved by the addition of urea in Oliva's system, namely preserving GFP activity while, at the same time, permitting RNA/RNA hybridization to occur is irrelevant to the appealed claims because neither RNA/RNA hybridization nor GFP activity are required to perform the claimed method.

In view of the above, the Appellants maintain their position that one of skill in the art would find no motivation to combine Brenner and Oliva.

In view of the foregoing discussion, the Applicants request that all remaining rejections be reversed and that the application be remanded to the Examiner with instructions to issue a Notice of Allowance.

Respectfully submitted,

Date: 12/30/05

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